

Prevalence and Spectrum of Germline Variants in Non–Small Cell Lung Cancer: Insights from a Large-Scale CARIS Analysis

Nirmal Choradia¹, Wen Gu², Abdul R. Naqash¹, Muhammad Furqan¹, Sharon Wu², Joanne Xiu², Misty Dawn Shields³, Biagio Ricciuti⁴, Hossein Borghaei⁵, Balazs Halmos⁶, George W. Sledge, Jr.², David Spetzler², Raid Aljumaily¹

¹The University of Oklahoma Health Sciences, Oklahoma City, OK · ²Caris Life Sciences, Phoenix, AZ · ³Indiana University Melvin & Bren Simon Comprehensive Cancer Center, Indianapolis, IN · ⁴Dana-Farber Cancer Institute, Boston, MA · ⁵Fox Chase Cancer Center, Philadelphia, PA · ⁶Montefiore Einstein Comprehensive Cancer Center, Bronx, NY

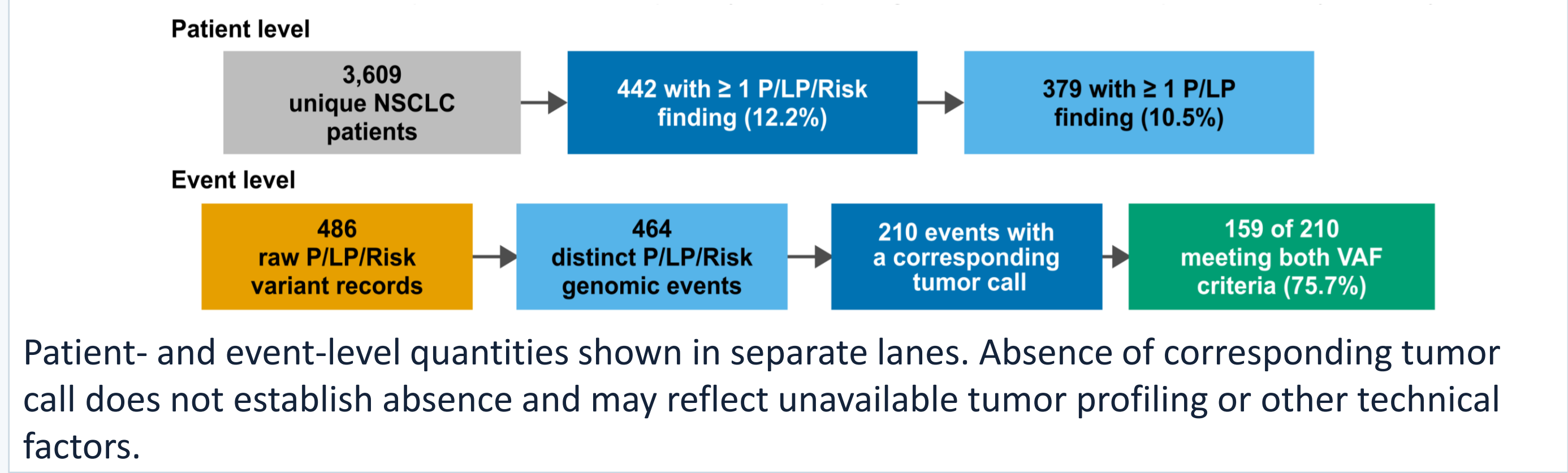
INTRODUCTION

- Tobacco exposure is a major cause of NSCLC, but inherited susceptibility may also contribute to risk in a subset of patients.
- Germline (hereditary) testing is not routine in NSCLC, so potentially relevant inherited variants may go unrecognized.
- We characterized buffy-coat germline findings in a real-world NSCLC blood-based profiling cohort and evaluated corresponding variants in linked solid-tumor profiles.

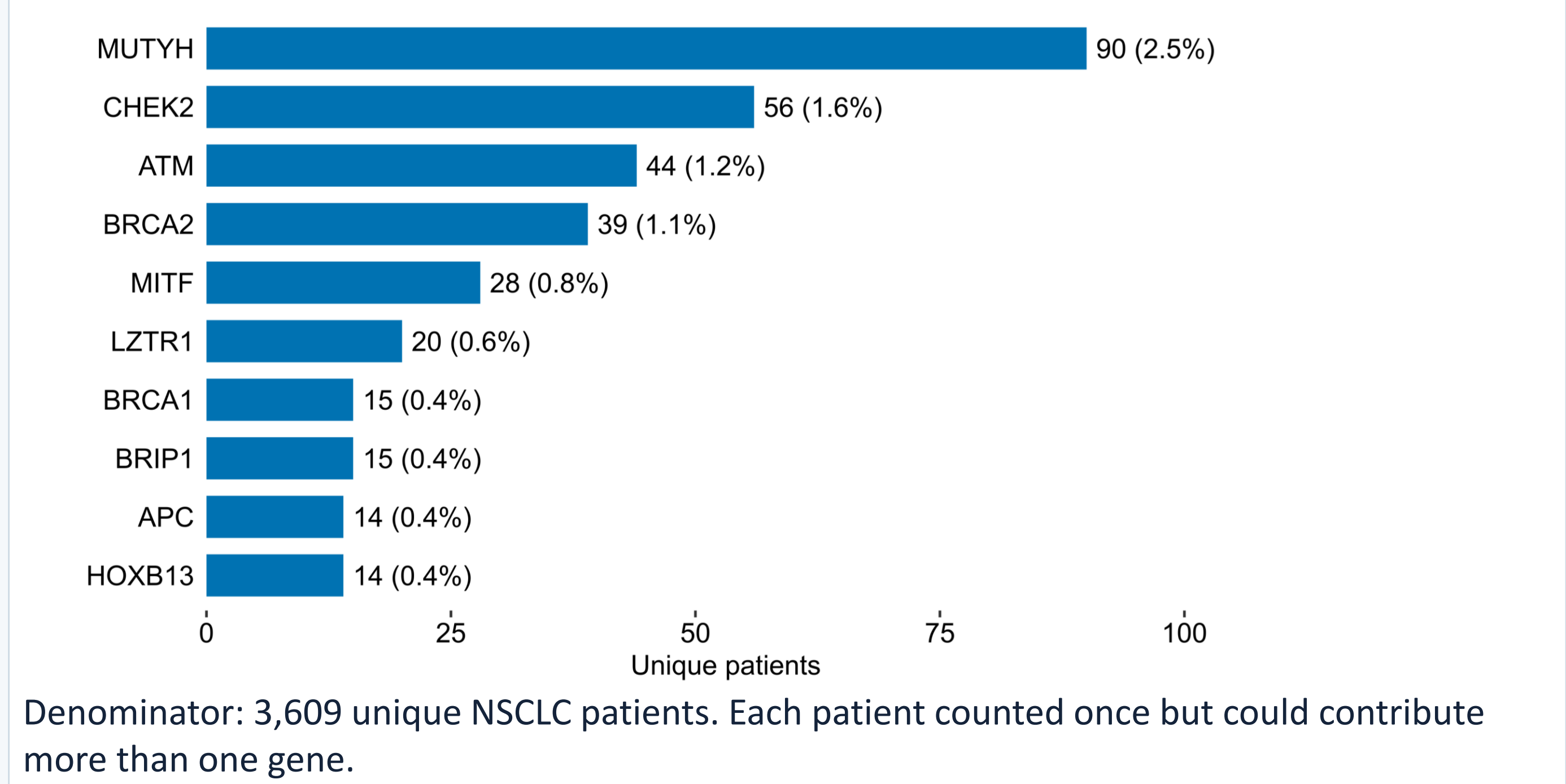
METHODS

- Design:** Retrospective patient-level analysis of the current NSCLC blood-based profiling extract. Linked solid-tumor profiles were evaluated when available.
- Germline findings:** Buffy-coat findings were categorized as pathogenic, likely pathogenic, risk allele, VUS, benign, or likely benign. Patient-level P/LP/Risk status was defined by the presence of at least one qualifying finding.
- Demographic analysis:** The primary comparison included patients with at least one P/LP/Risk finding versus patients whose classified findings were limited to benign/likely benign. Patients with only VUS, unknown, Intermediate, null, or other findings were excluded. P/LP/Risk status took priority when patients had findings from multiple categories.
- Linked tumor analysis:** Germline and tumor variants were matched within patient using genomic coordinates, with gene and protein change used as a fallback.
- Statistics:** Age, sex, race, and tumor SBS4 (smoking signature) burden were evaluated using unadjusted comparisons and multivariable logistic regression. The primary comparison included 875 patients, and the adjusted complete-case model included 369 patients.

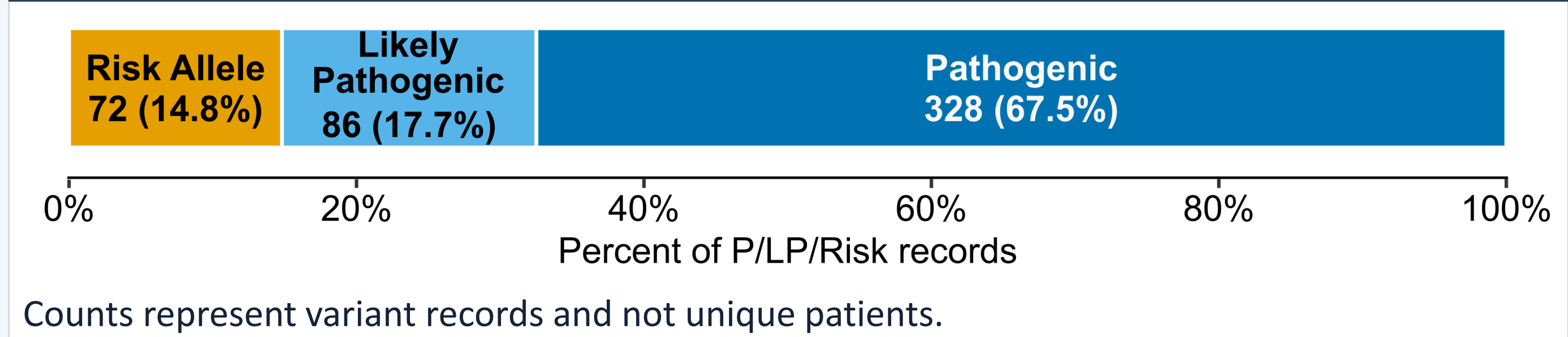
NSCLC COHORT AND ANALYTIC FLOW



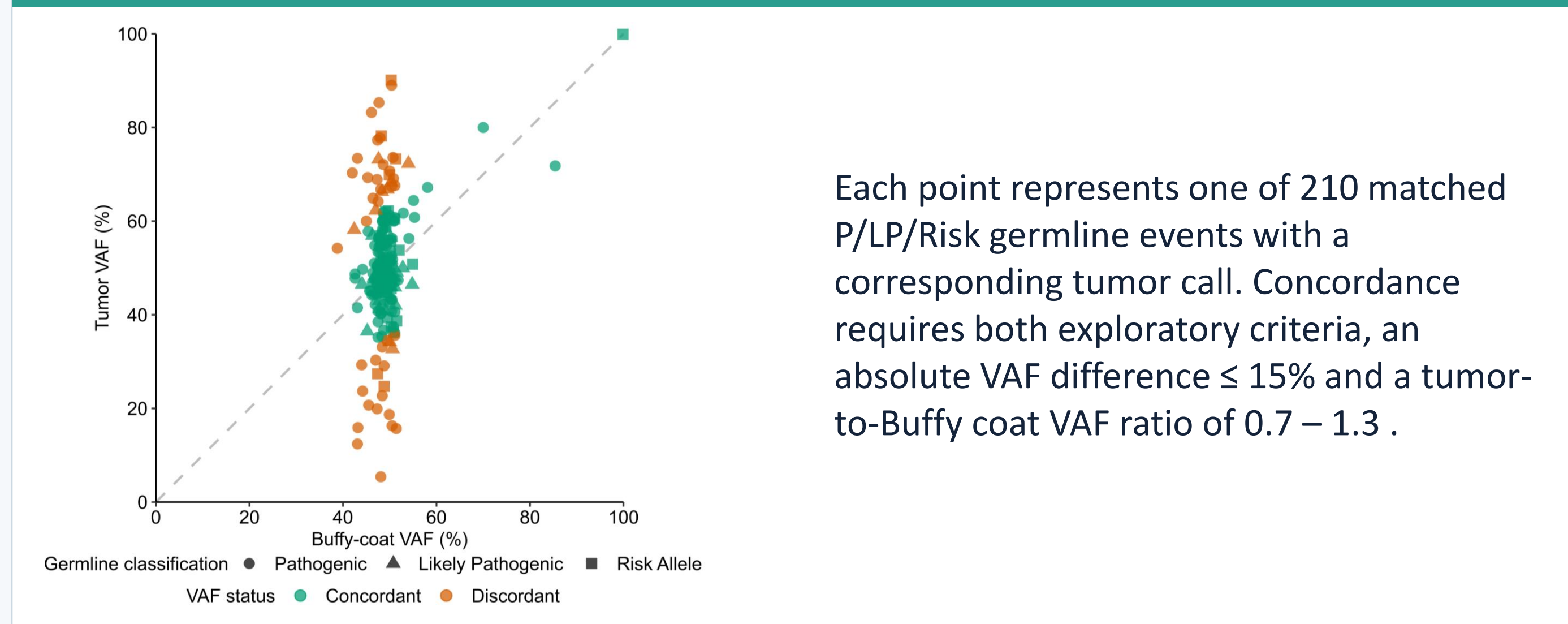
MOST FREQUENT P/LP/RISK GENES (by unique patient count)



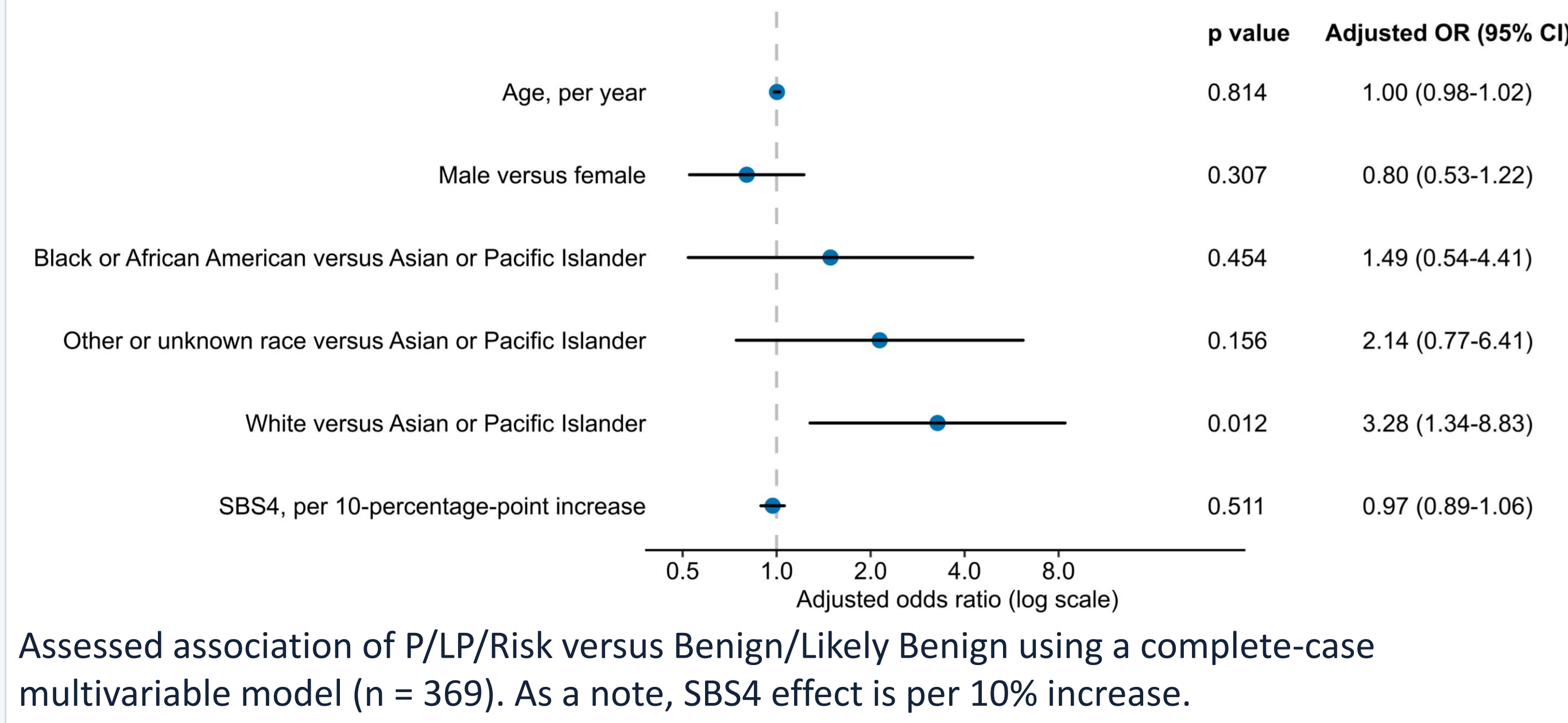
COMPOSITION OF 486 P/LP/RISK VARIANTS



BUFFY COAT VERSUS TUMOR VAF



ADJUSTED ASSOCIATIONS WITH P/LP/RISK STATUS



Tumor SBS4 burden was not associated with P/LP/Risk status

- In the primary patient-level comparison of P/LP/Risk versus benign/likely benign findings, the multivariable complete-case model included 369 patients. Tumor SBS4 burden was not independently associated with P/LP/Risk status (adjusted OR 0.97 per 10 percentage-point increase; 95% CI 0.89 to 1.06; $p = 0.511$). Age and sex were also not significant. White race was associated with higher odds of P/LP/Risk status relative to Asian or Pacific Islander patients (adjusted OR 3.28; 95% CI 1.34 to 8.83; $p = 0.012$).
- SBS4 is an imperfect tumor-based proxy for tobacco-related mutagenesis and may not capture all current or former smoking exposure; therefore, the absence of SBS4 should not be used to infer the absence of clinically relevant germline findings.

CONCLUSIONS

- P/LP/Risk germline findings involved several cancer-predisposition and DNA damage-repair genes in this NSCLC cohort.
- Linked solid-tumor profiling identified corresponding tumor variants for a subset of germline findings.
- These descriptive findings support further study of germline-evaluation strategies in NSCLC and of criteria for referral to genetic counseling.

CLINICAL IMPLICATIONS AND NEXT STEPS

- Blood-based profiling with buffy-coat analysis may identify patients P/LP findings in established hereditary cancer genes who warrant genetic counseling and confirmatory germline testing.
- Such findings may prompt genetic counseling and cascade testing of at-risk relatives.
- Next steps include assessing germline findings in comparison to all CARIS Assure tests to get rate of germline variants in NSCLC and understanding the cohort of NSCLC cancer patients and families likely to benefit from germline and cascade testing